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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/737,262	12/15/2003	Leonidas Stefanis	5199-26	6898

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/737,262	STEFANIS ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *28-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-58* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks filed 20 December 2005 have been entered. Claims 1 – 58 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group II in the reply filed on 20 December 2005 is acknowledged. The traversal is on the ground(s) that

1) Groups I and II should be rejoined as Group I is a process specially adapted for the production of the product of Group II and

2) Groups II and III should be rejoined because the product cannot be used for any process other than the screening assays of Group III.

With respect to 1) above, applicant's arguments are persuasive. No product other than those of Group II could be made by the process of Group I. Thus Groups I and II will be rejoined.

With respect to 2) above, applicant's arguments have been fully considered but are not persuasive. The products of Group II, which can made by the process of Group I, are suitable for the expression of the A53T mutant protein, as pointed out in the paragraph spanning pp. 2 – 3 of the restriction requirement. The utility of this specific mutant form of the alpha-synuclein protein was widely recognized in the prior art as a target for anti-Parkinsonian drugs and in fact *in vitro* screening methods using the mutant protein had been described. As the products of Group II can be used for a different process, namely for production of mutant A53T synuclein protein, which is then useful in screening assays, Groups II and III are patentably distinct and thus it is appropriate to maintain the restriction requirement between them. Furthermore, when an application contains claims to a product as well as methods of making and using the product, it is proper to require restriction between the product and the method of making it on the one hand and the method of using the product on the other. See MPEP § 806.05(i).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 28 – 58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 20 December 2005.

4. Claims 1 – 27 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, from which claims 2 – 23 depend, recite "a dopaminergic cell line" in the preamble. However the steps of claim 1 instruct the artisan to introduce a vector into a PC12 cell. PC12 cells are not dopaminergic cells, as a subset of neurons are dopaminergic whereas PC12 cells are derived from tumors of the adrenal gland and as such are not neurons. Furthermore dependent claim 17 recites the limitation "exhibits dopaminergic dysfunction"; it is unclear how a cell which is not a neuron can exhibit dopaminergic dysfunction.

6. Claims 7 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "the promoter" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC §§ 102 and 103

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 7 and 9 – 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Stefanis (15 December 2001. Journal of Neuroscience 21:9549-9560). For the sake of clarity, this Stefanis reference is referred to as Stefanis (2001A).

Stefanis (2001A) teaches methods of making PC12 cells stably expressing the human A53T mutant synuclein protein and the wild-type protein. The specific steps used to make the PC12 cells are described on p. 9550, first column and meet the limitations of claim 1. Specifically, Stefanis (2001A) teaches PCDNA3 plasmid vector comprising nucleic acid encoding the A53T mutant alpha synuclein protein, as it relates to claims 2 – 4 and 9 – 11. The pcDNA3 vector inherently has a neomycin resistance gene as a selectable marker (see p. 9550, first column), as it relates to claims 2 – 4. Stefanis (2001A) also teaches selecting the cells on neomycin, as it relates to claims 5 and 6, as well as introducing the vector to the cells by electroporation, as it relates to claims 12 – 13. The pcDNA3 vector also has an SV40 promoter, which is induced in the presence of T-antigen, thereby meeting the limitation of claim 7. Stefanis (2001A) teaches that compared to the control cells, the mutant cells show enhanced cellular degeneration in the absence of differences in apoptosis (p. 9552, first column), cytoplasmic ubiquitinated aggregates (p. 9552, second column), reduced proteasomal activity and chymotrypsin activity(p. 9553, second column), absence of dense core granules (p. 9553, final paragraph), defective dopamine release (p. 9554, second column), and lysosomal dysfunction (p. 9555, second column). Thus the cells have the properties recited in claims 14 – 27. Furthermore Stefanis (2001A) teaches that the cells are useful as a model for Parkinson's disease (see p. 9558, second column, final sentence), as it relates to claims 26 - 27.

8. Claims 1 – 7 and 9 – 27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stefanis (1999. Neurology 52(6) Supplement 2:A4).

Stefanis teaches PC12 cells (that is, products) stably expressing the human A53T mutant synuclein protein (see Design/Methods). Claims 24 and 25 recite specific inherent characteristics of the cell line. Many of these, including increases in neuronal degeneration (which is synonymous with non-apoptotic cell death recited in claim 24) and increased ubiquitinated inclusion bodies (i.e. aggregates, recited in claim 25) are explicitly taught in the Results section of the reference. Furthermore Stefanis compared the cell lines expressing the mutant protein to those expressing the wild-type protein. As both inventors are listed as authors of the Stefanis reference, and the prior art reference teaches the claimed product, it is assumed to have the recited properties absent evidence to the contrary. See MPEP § 2112. Thus claims 24 and 25 are anticipated by the reference.

Claim 1 recites the steps of introducing an expression vector into a cell and isolating PC12 cells stably expressing A53T. Stefanis teaches isolating PC12 cells stably expressing the A53T and wild-type forms of human alpha synuclein. The vector used was the plasmid vector pCDNA3 (see Design/Methods), which meets the limitations of claims 9 - 11. While the reference does not recite the explicit step of introducing the vector to the cells, this necessarily has to be done to get the vector into the cells, thus the reference teaches the method of claim 1. The reference is silent as to whether or not the vector comprises a sequence encoding a selectable marker gene in general or neo in particular. However, as set forth in the rejection over Stefanis (2001A) above, pcDNA3 inherently has a neo marker. Thus the specific limitations recited in claims 2 – 4 are inherent in the teachings of Stefanis (1999) even though they are not explicitly recited. Claim 7 is limited to an inducible promoter; as set forth in the rejection over Stefanis (2001A) above, the SV40 promoter is present on the pcDNA3 vector and is inducible by T-antigen.

Claims 14 – 23 and 26 – 27 recite specific properties of the cell line created by the method. The reference teaches that compared to cells expressing wild-type synuclein, those expressing the mutant form "manifest morphological alterations and enhanced neuronal degeneration In addition, they demonstrate a marked increase in ubiquitin ... largely in the form of inclusion bodies. ...[t]he A53T mutation confers an abnormal function to alpha-synuclein, leading to its aggregation, ubiquitination and eventually to cellular degeneration." (see Results

and Conclusion paragraphs). Thus the reference explicitly teaches the properties recited in claims 15 and 22. The reference is silent as to whether or not the cells made by this method have the properties recited in claims 14, 16 – 21, and 23. However as these are inherent properties of the product, it is assumed to have the recited properties absent evidence to the contrary. See MPEP § 2112. The examiner notes that the Stefanis (2001A) reference appears to provide evidence that the cell lines first disclosed in Stefanis (1999) do in fact have each and every property recited in claims 14 – 27. Additionally, Stefanis (1999) teaches that the cells are useful as a model for Parkinson's disease, as it relates to claims 26 – 27.

The examiner cannot determine if the experiments described in the Stefanis (1999) reference comprised growing the cells on neomycin, as it relates to claims 5 and 6. However, as the vector used comprises a neomycin resistance gene, and selection of cell lines with antibiotics appropriate to the vector were well-known in the prior art, this feature appears to be either anticipated by, or obvious over, Stefanis. Again the examiner notes that Stefanis (2001A), which lists both inventors, appears to be drawn to identical material and also teaches growing the cells on neomycin for selection. Similarly, the examiner cannot determine if the Stefanis reference (1999) used electroporation, as it relates to claims 12 – 13, for introducing the vector to the cells. However, the method of electroporation for transferring plasmid vectors to cells was well known, and this method was described in Stefanis (2001A), which appears to be drawn to identical material.

9. Claims 1 – 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefanis (1999) and Stefanis (February 2001. Journal of Neurochemistry 76:1165 – 1176, cited on IDS filed 30 July 2004; for the sake of clarity this reference is referred to as Stefanis 2001B) as applied to claims 1 – 6 and 9 – 25 above, and further in view of Tanaka (15 April 2001. Human Molecular Genetics 10(9):919-926, cited by applicant on IDS filed 30 July 2004).

The reasons why Stefanis (1999) and Stefanis (2001B) either anticipate or render obvious claims 1 – 7 and 9 – 27 are set forth in the rejections under 35 USC §§ 102 and 103 above. However neither reference teaches tetracycline inducible promoters recited in claim 8.

Tanaka teaches the method of making PC12 cells which express mutant alpha synuclein under the control of the tetracycline inducible promoter (recited in claims 7 and 8; see RESULTS, beginning on p. 920 and Materials and Methods on p. 924). Tanaka teaches the use of inducible promoters in such a system is advantageous because it allows for repression of the toxic mutant synuclein during clonal selection and permits comparing cellular physiology

before and after inducing the transgene, thereby obviating the need for a separate control cell line. However Tanaka teaches the A30P, not A53T, mutation in human synuclein.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Stefanis (1999) and Stefanis (2001B) to include the tetracycline inducible promoter from Tanaka, with a reasonable expectation of success. The motivation to do so would be to take advantage of the specific benefits offered by the system, including decreased toxicity to the cell line and obviating the need for control cells.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DK

Daniel E. Kolker, Ph.D.
February 8, 2006

ROBERT C. HAYES, PH.D.
PATENT EXAMINER